CLAIMS

1. A method of treating patients who have diseases characterized bone loss comprising the step of administering to said patient an amount of a TRANCE/RANK inhibitor effective to inhibit osteoclastogenesis and/or osteoclast function.

2. The method of claim 1 wherein said TRANCE/RANK inhibitor is a compound having the Formula I wherein:

R_1 and R_2 are, independently, selected from the group consisting of -H, -OCH_3, -CH_2CH_3, -*t*-butyl, 3-carboxy-4-chlorophenylamino, -N-$(CH_2CH_2OH)_2$, and -O(O)C-Ph;

R_3 is selected from the group consisting of -H, ethyl, -OCH_3, -Cl, Br, F, 3-carboxy-4-chlorophenylamino, -N-$(CH_2CH_2OH)_2$, -*t*-butyl, and -OC(O)-Ph, and is not limited to attachment at any certain position on the phenyl ring to which it is attached; and

R_4 is selected from the group consisting of -Br,-Cl, and -F.

3. The method of claim 2 wherein R_3 is attached at either the 1 or 4 position of the phenyl ring.

4. The method of claim 1 wherein

R_1 , R_2, and R_3 are -OCH_3, R_3 is attached at the 4 position, R_4 is -Cl;

R_1 and R_2 are methyl, R_3 is ethyl, attached at the 4 position, R_4 is -Cl

R_1 and R_2 are -OCH_3, R_3 is -Cl, attached at the 2 position, R_4 is -Cl;

R_1 and R_2 are -OCH_3 and R_3 is H, R_4 is -Cl;

R_1 is H, R_2 and R_3 are 3-carboxy-4-chlorophenylamino, and R_3 is attached at the 4 position, R_4 is -Cl;

R_1 and R_2 are -N$(CH_2CH_2OH)_2$, R_3 is Cl, attached at the 4 position, R_4 is -Cl;

R_1, R_2, and R_3 are *t*-butyl, R_3 is attached at the 4 position, R_4 is -Cl;

R_1 is -OCH_3, R_2 and R_3 are H, R_4 is Cl; or

R_1, R_2, and R_3 are benzoate, R_3 is attached at the 4 position, R_4 is -Br.

5. The method of claim 1 wherein said TRANCE/RANK inhibitor is selected from the group consisting I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H and I-I.

6. The method of claim 1 wherein said TRANCE/RANK inhibitor is a compound having the Formula II wherein:

R_1 is selected from the group consisting of -diphenylchloro methyl, -di(4-chlorophenyl)chloro methyl, and 4-(diphenylchloromethyl)phenyl; and

R_2, R_3, R_4 are independently selected from the group consisting of -Br, -Cl, and -F.

7. The method of claim 6 wherein R_2, R_3, R_4 are each -Cl.

8. The method of claim 1 wherein the TRANCE/RANK inhibitor is selected from the group consisting compounds II-A, II-B, II-C and II-D.

9. The method of claim 1 wherein said inhibitor is a compound having Formula III wherein:

R_1 = (NO_2), $O(CO)CH_3$, OH, $O(CO)CH_3$, $O(CO)(CH_2)_2COOH$, $O(CO)CH_2Br$, $O(CO)CH_2Cl$, $O(CO)CH_2N(CH_3)_3$, or OC_5H_9O;

R_2 = $CH_2O(NO_2)$, CHO, $CH_2O(NO_2)$, CN, CH_3, COOH, CHNOH, $CH_2O(CO)(CH_2)_2COOH$, $CHN(NH)CONH_2$, $CHN(NH)C_6H_5$, $CHN(CH_2)C_6H_5$, $CH_2N(CH_2)_2OH$, $CH_2NC_6H_5$, or $CH_2N(NH)CSNH_2$;

R_3 = OH, or H;

R_4 = CH_3;

R_5 = OH;

R_6 = $C_4H_3O_2$, $N(NHCO)C_6H_4Cl$, $N(NHCO)C_6H_4F$, COOH, O, $COCH_3$, $CH(CH_3)(CH_2)_2COOH$, $CH(CH_3)(CH_2)_2COOCH_3$, $O(CO)C_6H_5$, or OH;

R_7 = $O(CO)CH_2N(CH_3)_3$, or $O(CO)CH_3$;

R_8 = OH;

R_9 = O, or OH; and

R_{10} = O.

10. The method of claim 1 wherein the inhibitor is selected from the group consisting compounds III-1 to III-31.

11. The method of claim 1 wherein said inhibitor is a compound having Formula IV wherein:

$R_1 = O(CO)(CH_2)_2COOH$, or $O(CO)CH_2Br$; and

$R_2 = O(CO)(CH_2)_2COOH$, or $O(CO)CH_2Br$.

12. The method of claim 1 wherein the inhibitor is selected from the group consisting compounds IV-1 and IV-2.

13. The method of claim 1 wherein said inhibitor is a compound having Formula V wherein:

$R_1 = O$, OH, or $O(CO)CH_3$;

$R_2 = O(CO)CH_3$, OH, $CO(CH_3)$, or $CO(CH_2)O(CO)CH_3$;

$R_3 = CH_3$, or OH; and

$R_4 = O(CO)CH_2C_6H_4I$, or CH_3.

14. The method of claim 1 wherein the inhibitor is selected from the group consisting compounds V-1 and V-5

15. The method of claim 1 wherein said inhibitor is a compound having Formula VI wherein:

$R_1 = O(CO)CH_3$, OH, or $O(CO)(CH_2)_2COOH$;

$R_2 = CH_3$;

$R_3 = O$, or OH;

$R_4 = CH_3$;

$R_5 = C_9H_{13}COCH_3$, $C_9H_{13}(CH_2CH_3)(CH_2OH)$, $C_9H_{13}(CH_2CH_3)(CH_2OCOCH_3)$, $C_9H_{13}(CH_2CH_3)(CH_2OCO(CH_2)_2COOH)$, $C_9H_{13}(CH_2CH_3)(COOH)$, or $C_8H_7O(CH_3)(C_4H_9OCH_3)$;

$R_6 = CH_3$;

R_7 = O, or H;

R_8 = CH_3;

R_9 = $(CH_3)_2$;and

R_{10} = Br.

16. The method of claim 1 wherein the inhibitor is selected from the group consisting compounds VI-1 and VI-11.

17. The method of claim 1 wherein the inhibitor is selected from the group consisting compounds VII, VIII IX, X, XI and XII.

18. The method of claim 1 wherein the inhibitor is a peptide having the formula:

$R_1 - R_2 - R_3 - R_4 - R_5$

wherein:

R_1 is 1-5 amino acid residues;

R_2 is a linking amino acid residue;

R_3 is selected from the group consisting of: DRGWA (SEQ ID NO:1); DGDLAT (SEQ ID NO:2); SDFATE (SEQ ID NO:3); VTKTSIKIPSSH (SEQ ID NO:4); TKTSIKIPSSH (SEQ ID NO:5); KTSIKIPSSH (SEQ ID NO:6); YWSNSEF (SEQ ID NO:7); YWNSE (SEQ ID NO:8); PDQDAP (SEQ ID NO:9); PDSWH (SEQ ID NO:10); SKEL (SEQ ID NO:11); EIEF (SEQ ID NO:12); SRSGHS (SEQ ID NO:13); RFQEEIKENTKNDKQ (SEQ ID NO:14); TSYPD (SEQ ID NO:15); KENTK (SEQ ID NO:16); and conservatively substituted derivatives thereof;

R_4 is a linking amino acid residue;

R_5 is 1-5 amino acid residues; and

wherein R_2 and R_4 are bound to each other, thereby forming a cyclic portion which includes R_2, R_3 and R_4 with R_1 and R_5 forming exocyclic portions, and one or both of R_1 and R_5 comprising at least one tyrosine or phenylalanine.

19. The method of claim 1 wherein the inhibitor is selected form the group consisting of SEQ ID NOs:20-34.

20. The method of claim 19 wherein the inhibitor is selected from the group consisting of: SEQ ID NOs:20-30 with amidated C termini

[H]-YC DRGWA CY-[NH2]

[H]-YC DGDLAT CY-[NH2]

[H]-YC SDFATE CY-[NH2]

[H]-YC VTKTSIKIPSSH CY-[NH2]

[H]-YC KTSIKIPSSH CY-[NH2]

[H]-YC YWSNSEF CY-[NH2]

[H]-C YWNSE CY-[NH2]

[H]-YC PDQDAP CY-[NH2]

[H]-YC PDSWH CYDE-[NH2]

[H]-YC SKEL CYVKQE-[NH2]

[H]-YC EIEF CYKHR-[NH2]

and SEQ ID NO:S 31-34

TR-LSS YC SRSGHS CY

TR-LRQ YC RFQEEIKENTKNDKQ CY

TR-LTI YC TSYPD CI

TR-LED RYQEEC KENTK CDKQ.

21. A method of modulating dendritic cell maturation, T cell proliferation, and/or CD40 receptor systems in an individual comprising the step of administering to said individual an amount of a TRANCE/RANK inhibitor effective to modulating dendritic cell maturation, T cell proliferation, and/or CD40 receptor systems.

22. The method of claim 21 wherein said TRANCE/RANK inhibitor is a compound having the Formula I wherein:

R_1 and R_2 are, independently, selected from the group consisting of -H, -OCH_3, -CH_2CH_3, -*t*-butyl, 3-carboxy-4-chlorophenylamino, -N-$(CH_2CH_2OH)_2$, and -O(O)C-Ph;

R_3 is selected from the group consisting of -H, ethyl, $-OCH_3$, -Cl, Br, F, 3-carboxy-4-chlorophenylamino, $-N-(CH_2CH_2OH)_2$, -*t*-butyl, and -OC(O)-Ph, and is not limited to attachment at any certain position on the phenyl ring to which it is attached; and

R_4 is selected from the group consisting of -Br,-Cl, and -F.

23. The method of claim 21 wherein R_3 is attached at either the 1 or 4 position of the phenyl ring.

24. The method of claim 21 wherein

R_1 , R_2, and R_3 are $-OCH_3$, R_3 is attached at the 4 position, R_4 is -Cl;

R_1 and R_2 are methyl, R_3 is ethyl, attached at the 4 position, R_4 is -Cl

R_1 and R_2 are $-OCH_3$, R_3 is -Cl, attached at the 2 position, R_4 is -Cl;

R_1 and R_2 are $-OCH_3$ and R_3 is H, R_4 is -Cl;

R_1 is H, R_2 and R_3 are 3-carboxy-4-chlorophenylamino, and R_3 is attached at the 4 position, R_4 is -Cl;

R_1 and R_2 are $-N(CH_2CH_2OH)_2$, R_3 is Cl, attached at the 4 position, R_4 is -Cl;

R_1, R_2, and R_3 are *t*-butyl, R_3 is attached at the 4 position, R_4 is -Cl;

R_1 is $-OCH_3$, R_2 and R_3 are H, R_4 is Cl; or

R_1, R_2, and R_3 are benzoate, R_3 is attached at the 4 position, R_4 is -Br.

25. The method of claim 21 wherein said TRANCE/RANK inhibitor is selected from the group consisting I-A, I-B, I-C, I-D, I-E, I-F, I-G, I-H and I-I.

26. The method of claim 21 wherein said TRANCE/RANK inhibitor is a compound having the Formula II wherein:

R_1 is selected from the group consisting of -diphenylchloro methyl, -di(4-chlorophenyl)chloro methyl, and 4-(diphenylchloromethyl)phenyl; and

R_2, R_3, R_4 are independently selected from the group consisting of -Br, -Cl, and -F.

27. The method of claim 26 wherein R_2, R_3, R_4 are each -Cl.

28. The method of claim 21 wherein the TRANCE/RANK inhibitor is selected from the group consisting compounds II-A, II-B, II-C and II-D.

29. The method of claim 21 wherein said inhibitor is a compound having Formula III wherein:

R_1 = (NO_2), $O(CO)CH_3$, OH, $O(CO)CH_3$, $O(CO)(CH_2)_2COOH$, $O(CO)CH_2Br$, $O(CO)CH_2Cl$, $O(CO)CH_2N(CH_3)_3$, or OC_5H_9O;

R_2 = $CH_2O(NO_2)$, CHO, $CH_2O(NO_2)$, CN, CH_3, COOH, CHNOH, $CH_2O(CO)(CH_2)_2COOH$, $CHN(NH)CONH_2$, $CHN(NH)C_6H_5$, $CHN(CH_2)C_6H_5$, $CH_2N(CH_2)_2OH$, $CH_2NC_6H_5$, or $CH_2N(NH)CSNH_2$;

R_3 = OH, or H;

R_4 = CH_3;

R_5 = OH;

R_6 = $C_4H_3O_2$, $N(NHCO)C_6H_4Cl$, $N(NHCO)C_6H_4F$, COOH, O, $COCH_3$, $CH(CH_3)(CH_2)_2COOH$, $CH(CH_3)(CH_2)_2COOCH_3$, $O(CO)C_6H_5$, or OH;

R_7 = $O(CO)CH_2N(CH_3)_3$, or $O(CO)CH_3$;

R_8 = OH;

R_9 = O, or OH; and

R_{10} = O.

30. The method of claim 21 wherein the inhibitor is selected from the group consisting compounds III-1 to III-31.

31. The method of claim 21 wherein said inhibitor is a compound having Formula IV wherein:

R_1 = $O(CO)(CH_2)_2COOH$, or $O(CO)CH_2Br$; and

R_2 = $O(CO)(CH_2)_2COOH$, or $O(CO)CH_2Br$.

32. The method of claim 21 wherein the inhibitor is selected from the group consisting compounds IV-1 and IV-2.

33. The method of claim 21 wherein said inhibitor is a compound having Formula V wherein:

R_1 = O, OH, or $O(CO)CH_3$;

R_2 = $O(CO)CH_3$, OH, $CO(CH_3)$, or $CO(CH_2)O(CO)CH_3$;

R_3 = CH_3, or OH; and

R_4 = $O(CO)CH_2C_6H_4I$, or CH_3.

34. The method of claim 21 wherein the inhibitor is selected from the group consisting compounds V-1 and V-5

35. The method of claim 21 wherein said inhibitor is a compound having Formula VI wherein:

R_1 = $O(CO)CH_3$, OH, or $O(CO)(CH_2)_2COOH$;

R_2 = CH_3;

R_3 = O, or OH;

R_4 = CH_3;

R_5 = $C_9H_{13}COCH_3$, $C_9H_{13}(CH_2CH_3)(CH_2OH)$, $C_9H_{13}(CH_2CH_3)(CH_2OCOCH_3)$, $C_9H_{13}(CH_2CH_3)(CH_2OCO(CH_2)_2COOH)$, $C_9H_{13}(CH_2CH_3)(COOH)$, or $C_8H_7O(CH_3)(C_4H_9OCH_3)$;

R_6 = CH_3;

R_7 = O, or H;

R_8 = CH_3;

R_9 = $(CH_3)_2$;and

R_{10} = Br.

36. The method of claim 21 wherein the inhibitor is selected from the group consisting compounds VI-1 and VI-11.

37. The method of claim 21 wherein the inhibitor is selected from the group consisting compounds VII, VIII IX, X, XI and XII.

38. The method of claim 21 wherein the inhibitor is a peptide having the formula:

$R_1 - R_2 - R_3 - R_4 - R_5$

wherein:

R_1 is 1-5 amino acid residues;

R_2 is a linking amino acid residue;

R_3 is selected from the group consisting of: DRGWA (SEQ ID NO:1); DGDLAT (SEQ ID NO:2); SDFATE (SEQ ID NO:3); VTKTSIKIPSSH (SEQ ID NO:4); TKTSIKIPSSH (SEQ ID NO:5); KTSIKIPSSH (SEQ ID NO:6); YWSNSEF (SEQ ID NO:7); YWNSE (SEQ ID NO:8); PDQDAP (SEQ ID NO:9); PDSWH (SEQ ID NO:10); SKEL (SEQ ID NO:11); EIEF (SEQ ID NO:12); SRSGHS (SEQ ID NO:13); RFQEEIKENTKNDKQ (SEQ ID NO:14); TSYPD (SEQ ID NO:15); KENTK (SEQ ID NO:16); and conservatively substituted derivatives thereof;

R_4 is a linking amino acid residue;

R_5 is 1-5 amino acid residues; and

wherein R_2 and R_4 are bound to each other, thereby forming a cyclic portion which includes R_2, R_3 and R_4 with R_1 and R_5 forming exocyclic portions, and one or both of R_1 and R_5 comprising at least one tyrosine or phenylalanine.

39. The method of claim 21 wherein the inhibitor is selected form the group consisting of SEQ ID NOs:20-34.

40. The method of claim 39 wherein the inhibitor is selected from the group consisting of: SEQ ID NOs:20-30 with amidated C termini

[H]-YC DRGWA CY-[NH2]

[H]-YC DGDLAT CY-[NH2]

[H]-YC SDFATE CY-[NH2]

[H]-YC VTKTSIKIPSSH CY-[NH2]

[H]-YC KTSIKIPSSH CY-[NH2]

[H]-YC YWSNSEF CY-[NH2]

[H]-C YWNSE CY-[NH2]

[H]-YC PDQDAP CY-[NH2]

[H]-YC PDSWH CYDE-[NH2]

[H]-YC SKEL CYVKQE-[NH2]

[H]-YC EIEF CYKHR-[NH2]

and SEQ ID NO:S 31-34

TR-LSS YC SRSGHS CY

TR-LRQ YC RFQEEIKENTKNDKQ CY

TR-LTI YC TSYPD CI

TR-LED RYQEEC KENTK CDKQ.

41. A peptide having the formula:

$$R_1 - R_2 - R_3 - R_4 - R_5$$

wherein:

R_1 is 1-5 amino acid residues;

R_2 is a linking amino acid residue;

R_3 is selected from the group consisting of: DRGWA (SEQ ID NO:1); DGDLAT (SEQ ID NO:2); SDFATE (SEQ ID NO:3); VTKTSIKIPSSH (SEQ ID NO:4); TKTSIKIPSSH (SEQ ID NO:5); KTSIKIPSSH (SEQ ID NO:6); YWSNSEF (SEQ ID NO:7); YWNSE (SEQ ID NO:8); PDQDAP (SEQ ID NO:9); PDSWH (SEQ ID NO:10); SKEL (SEQ ID NO:11); EIEF (SEQ ID NO:12); SRSGHS (SEQ ID NO:13); RFQEEIKENTKNDKQ (SEQ ID NO:14); TSYPD (SEQ ID NO:15); KENTK (SEQ ID NO:16); and conservatively substituted derivatives thereof;

R_4 is a linking amino acid residue;

R_5 is 1-5 amino acid residues; and

wherein R_2 and R_4 are bound to each other, thereby forming a cyclic portion which includes R_2, R_3 and R_4 with R_1 and R_5 forming exocyclic portions, and one or both of R_1 and R_5 comprising at least one tyrosine or phenylalanine.

42. The peptide of claim 41 wherein selected form the group consisting of SEQ ID NOs:20-34.

43. The peptide of claim 42 selected from the group consisting of: SEQ ID NOs:20-30 with amidated C termini

[H]-YC DRGWA CY-[NH2]

[H]-YC DGDLAT CY-[NH2]

[H]-YC SDFATE CY-[NH2]

[H]-YC VTKTSIKIPSSH CY-[NH2]

[H]-YC KTSIKIPSSH CY-[NH2]

[H]-YC YWSNSEF CY-[NH2]

[H]-C YWNSE CY-[NH2]

[H]-YC PDQDAP CY-[NH2]

[H]-YC PDSWH CYDE-[NH2]

[H]-YC SKEL CYVKQE-[NH2]

[H]-YC EIEF CYKHR-[NH2]

and SEQ ID NO:S 31-34

TR-LSS YC SRSGHS CY

TR-LRQ YC RFQEEIKENTKNDKQ CY

TR-LTI YC TSYPD CI

TR-LED RYQEEC KENTK CDKQ.